Histamine and Thyroid Hormone Function

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In an earlier paper in this journal I reviewed evidence suggesting that histamine serves as an important regulator of the microcirculatory system (Schayer, 1968). Since the metabolism of cells depends on their internal environment, and this depends on distribution of nutrients and removal of wastes through the capillaries, it seems evident that any hormone with a sustained circulatory effect could cause widespread secondary changes in metabolism.

Based on a microcirculatory function of histamine, a unified theory of glucocorticoid action has been described (Schayer, 1964b, 1967). It is the purpose of the present paper to consider if the histamine-microcirculation concept may help explain the complicated pattern of thyroid hormone effects on metabolism, growth and development.

Briefly, it will be postulated that a major function of thyroid hormone is for slowly developing adaptations of the circulatory system to environmental changes, and that many thyroid hormone effects are secondary to altered perfusion of tissues. There is no known *in vitro* effect of thyroid hormone which can reasonably explain any major number of the *in vivo* effects (Tata, 1964).

Observations on Thyroid Hormone Action

Any unifying theory of thyroid hormone action must attempt an explanation of the following observations in:

A. Homeothermic animals

1. There is a lag period between administration of thyroid hormone and appearance of its effects.
2. A moderate dose of thyroid hormone increases heat production (BMR); in young animals growth increases.
3. In cold adaptation the rise in thyroid output increases heat production but not growth.
4. The increase in BMR seems to relate to norepinephrine action and to induction of enzymes.
5. Thyroid hormone may sensitize the circulatory system to catecholamines, but this is not a consistent finding. The thyroid hormone-catecholamine relationship seems complex and confusing.
6. In hypothyroidism there is weakness, poor growth and development, cold intolerance and metabolic disturbances.

B. Amphibia

1. In tadpoles a moderate increase in thyroid hormone levels induces metamorphosis.
2. In mature amphibia even large doses of thyroid hormone have almost no effect.

Postulates for Circulatory Theory of Thyroid Hormone Action

1. A basic requirement for thyroid hormone may be for normal function of vascular smooth muscle and, possibly, of cardiac muscle. Thyroid hormone molecules may attach to receptors on these muscle cells and enhance their responsiveness to regulators of contraction and relaxation.

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2. The principal physiological regulators of vascular smooth muscle are the constrictors, norepinephrine and the unidentified intrinsic "tone-force." Opposing the constrictors are dilators; histamine is of primary importance in the small vessels.

3. Cardiac muscle may also be similarly affected; it is continuous with vascular smooth muscle and is influenced by the same vasoactive substances.

4. The lag period may be the time required for thyroid-induced changes in the contractile mechanism to become evident.

Possible Sequence of Events in Moderate Hyperthyroidism

1. Vascular smooth muscle is sensitized as described under Postulates.

2. Vasoconstrictor forces are potentiated in the arteries, larger arterioles and veins. However, in small vessels the dilator action of intrinsic histamine is enhanced, and precapillary sphincters open.

3. Through the process of "conducted vasodilatation" (Hilton, 1962) the arterial vessels relax, while the venous side remains partially constricted.

4. There is increased heart action, due to direct or indirect causes.

5. The overall circulatory pattern consisting of (a) strong heart action, (b) an open arterial system, (c) an open microcirculation, and (d) a partially constricted venous system permits a generalized overperfusion of tissues.

6. The abnormally rapid perfusion provides optimal nourishment to cells; metabolite-induced activation of enzymes occurs.

7. Responses of cells depend on their genetically predetermined capabilities (Pitt-Rivers and Tata, 1959). In mature homeotherms, which lack potential for growth, metabolic activation produces heat. In immature homeotherms, both energy production and growth occur.

Possible Role of Physiological Activation of Thyroid Hormone Output During Cold Adaptation

The increased energy production of moderate hyperthyroidism is useless in animals at room temperature, and heat must be dissipated. However, thyroid hormone output is increased as a homeostatic measure during cold adaptation; this is evidently the only known case of physiological activiation of the thyroid gland except in rapid growth and development.

1. Vascular smooth muscle is sensitized as in moderate hyperthyroidism.

2. The sympathetic nervous system is activated by cold stress; more norepinephrine is released, and vascular responsiveness to norepinephrine is enhanced.

3. The circulatory pattern is modified by increased sympathetic activity; blood flow to most vascular beds is reduced (Folkow, Heymans and Neil, 1965) and diverted to heart, lung and skeletal muscle.

4. Overperfusion occurs mainly in skeletal muscle. Increased metabolite levels induce activation of enzymes; in muscle they are primarily concerned with energy production. This energy is used to maintain body temperature.

The Thyroid-Norepinephrine Relationship in Cold Adaptation

Cold-acclimated animals show increased thyroid output (Barker, 1964) as well as sympathetic stimulation. There is considerable evidence that norepinephrine, not epinephrine, is of prime importance in regulating metabolic rate in cold-acclimated animals through the process of non-shivering thermogenesis (Hsieh and Carlson, 1957; Himms-Hagen, 1967). According to Himms-Hagen, "The mechanism by which the sympathetic nervous system produces this regulation is not at all understood."

The reasons for this lack of understanding are readily seen, for unlike epinephrine, norepinephrine has very little, if any, ability to stimulate metabolism directly. In fact, its only really potent action is vasoconstriction (Goodman and Gilman, 1965). Vasoconstriction, per se, cannot increase the metabolic rate, since it markedly reduces nutritive blood flow in skeletal muscle; muscle is the major site of thyroid-induced increase in BMR. Accordingly, it seems necessary either to postulate a wholly obscure energy-producing function for norepinephrine, or to enquire whether sympathetic vasoconstriction, suitably modified, might lead to increased metabolic rates.

A possible clue is the abundant flow of blood through skeletal muscle during exercise, despite an activated sympathetic nervous system. A dilator mechanism opens the small vessels in muscle, the arterial side relaxes reflexly, and the circulatory picture described under Postulates develops. I believe the dilator mechanism to involve histamine (Schayer, 1964a, 1968).

In cold adaptation, dilatation at the level of the small vessels could presumably produce a similar circulatory picture. Norepinephrine may activate compensatory production of histamine in microvascular smooth muscle cells of skeletal muscle. We have observed norepinephrine induction of histidine decarboxylase in skeletal muscle, skin and lung of mice, but not in other tested tissues (Schayer, 1960, 1962). Leblanc (1963) assayed urine of rats during cold adaptation and found large increases in norepinephrine and histamine levels, the latter possibly being of microvascular origin.

Effect of Increased Thyroid Hormone Levels in Amphibia

In the tadpole, the enzymatic potential of cells is oriented toward metamorphosis. If thyroid hormone causes a generalized overperfusion

of tissues, the abundant supply of blood-borne nutrients, perhaps including certain rate-limiting substances, may trigger metabolite-induced activation of many enzymes and permit cells to achieve their fullest potential consistent with other existing environmental factors.

In the mature amphibian, however, further growth or development is not possible. Since the cells evidently have no enzymic mechanisms significantly concerned with heat production, thyroid hormone, even in large doses, has almost no effect in a frog (Barker, 1964).

The Thyroid Hormone-Catecholamine Relationship

Many studies have related thyroid hormone effects to potentiation of action of catecholamines, particularly norepinephrine; however, there are conflicting reports, and the picture is confusing (Brewster et al., 1956; Barker, 1964; Harrison, 1964; Theilen and Wilson, 1967).

If it is assumed that thyroid hormone has a primary circulatory action and involves histamine, experimental findings on thyroid-catecholamine interaction might be complicated for the following reasons:

1. Histamine is an antagonist of norepinephrine; it is found in high concentrations in perivascular mast cells and in sympathetic nerves.

2. Injection or release of catecholamines may release preformed histamine (Beck, 1965).

3. Injection or release of catecholamines may increase the rate of histamine formation (Schayer, 1960, 1962).

4. The status of the adrenal cortex is of great importance to the experimental outcome; glucocorticoids reduce microcirculatory actions of histamine and potentiate those of catecholamines (Schayer, 1964b, 1967).

In addition, other homeostatic mechanisms, not included in the present thesis, are involved.

Specificity of Thyroid Hormone Action

In liver, the tissue most frequently studied for induction of enzymes, a number of hormones, including thyroid hormone, initiate the same sequence of events in early stages of protein synthesis, i.e., increased nuclear RNA polymerase activity and increased RNA synthesis. Subsequently, however, there is some discrimination, for the pattern of activated enzymes differs for each hormone.

Although a solution to this problem is undoubtedly difficult, the importance of circulatory factors, at present often overlooked by biochemists, must certainly be recognized. Some of these factors are:

1. Hepatic cells are not metabolically identical; the metabolic status of each cell depends on its local nutrient environment, and this varies with the position of the cell along the sinusoid.

2. Any factor which alters liver hemodynamics may alter local nutrient supplies and, hence, affect the level of activity of hepatic enzymes (Brauer, 1963; Rappaport, 1963).

3. Hormones may release histamine and other vasoactive substances (Szego, 1965) or interact with vasoactive substances through potentiation, inhibition, impaired synthesis, or other means. Presumably a sufficient dose of any hormone will cause catecholamine release.

4. Because of the complexity of the hepatic vascular system and the heterogeneous metabolic characteristics of the hepatic cells, metabolic changes arising from circulatory disturbances would be complex and, at present, unpredictable.

In addition, some hormones may affect nutrient levels by other means, e.g., by changing permeability of cell or organelle membranes in liver or in other tissues.

Thyroid hormone activates hepatic respiratory enzymes; the fact that these enzymes are localized in a particular region, Zone 1 of the liver acinus (Rappaport, 1963), may be relevant to the apparent specificity of the hormone.

In skeletal muscle, the tissue which undergoes the greatest increase in thyroid-induced BMR, there seems to be no problem of specificity; evidently no other hormone produces comparable effects in muscle.

Hypothyroidism

In terms of the present thesis, vascular responsiveness would be subnormal in hypothyroid animals. The symptoms, e.g., weakness, poor growth and development, cold intolerance and metabolic disturbances, could result from impaired nutritive blood flow and inadequate cell nutrition.

Summary of Evidence and Arguments Supporting a Primary Vascular Function for Thyroid Hormone

1. Many investigators have reported that excessive levels of thyroid hormone sensitize the cardiovascular system to catecholamines (Brewster et al., 1956; Barker, 1964).

2. During increased thyroid output in cold acclimation, norepinephrine is much more potent than epinephrine in increasing nonshivering thermogenesis (Hsieh and Carlson, 1957; Himms-Hagen, 1967.) Yet norepinephrine is almost exclusively a vasoconstrictor; unlike epinephrine, it has very little ability to stimulate metabolism directly.

3. Heat production in hyperthyroid animals is reduced by several types of drugs which reduce catecholamine effects.

4. In hyperthyroid animals adrenergic blockade reduces the BMR to euthyroid levels, not to hypothyroid levels. This and other evidence indicate that metabolic effects of thyroid hormone cannot

be entirely attributed to action of adrenergic amines (Barker, 1964). The present view suggests that vasoconstriction is essential for increased BMR, but that there is an alternative to mediation by catecholamines. A vasoconstrictor "tone-force" exists which is not referable to any known blood-borne substance (Barcroft, 1963) and which is unaffected by any drug acting through reduction of catecholamine action. This tone-force is particularly strong in skeletal muscle, the major site of energy production in hyperthyroidism (Tata, 1964).

5. From the evidence outlined above, it seems highly probable that thyroid-induced heat production relates to vasoconstriction. However, vasoconstriction, per se, strongly reduces nutritive blood flow in a resting animal. In order to provide extra energy for prolonged periods, nutritive blood flow must rise above resting levels. Accordingly, to reconcile thyroid-induced vasoconstriction with the observed activation of metabolism, there must also be a mechanism for opening precapillary sphincters.

6. Thyroid hormone sensitizes animals to the lethal effects of histamine (Spencer and West, 1961). Since this enhanced sensitivity is blocked by glucocorticoids, it seems probable that the point of sensitization is microvascular smooth muscle.

7. If thyroid hormone does sensitize precapillary sphincters to histamine and histamine does relax sphincters during exercise, then thyroid hormone excess plus exercise may yield an exceptionally great blood flow in skeletal muscle. This is actually observed; hyperthyroid patients performing a standard exercise show a markedly exaggerated postexercise hyperemia (Barcroft, 1963).

8. Metamorphosis in amphibians presumably requires activation of a vast number of metabolic processes, all within a relatively short period of time. Since elevated nutrient levels are a primary stimulus for enzyme induction and for a general acceleration of cell metabolism, and since the availability of *all* normal nutrients could be markedly enhanced by the circulatory pattern previously described, it seems quite reasonable that the transformation of a tadpole into a frog could result from the sequence: thyroid hormone → increased local blood flow → elevation of nutrient levels in cells → triggering of enzyme activation → metamorphosis. In contrast to this simple picture, it is difficult to envisage how a primary hormone action directed, for example, toward some change in carbohydrate or protein metabolism or to an effect on the permeability of certain cells to certain nutrients, could produce such a complex transformation.

9. Thyroid hormone increases the metabolic rate of skeletal muscle, heart, liver, kidney, salivary gland, gastric mucosa and skin but has little, if any, effect on a number of other tissues, e.g., spleen, lymph nodes, thymus, gastrointestinal smooth muscle, lung, gonads. Yet thyroid hormone penetrates all these tissues to a roughly comparable extent (Barker, 1964).

Since there is no major metabolic distinction between these two groups of tissues, the data are not readily explained by a direct metabolic action of thyroid hormone. However, these tissues may show major differences in circulatory responses. For example, different effects of vasoactive substances on capillary blood flow might underlie group differences.

10. Thyroid hormone causes brain changes but evidently does not cross the blood brain barrier. If this is so, a direct action of the hormone on cells of the central nervous system seems unlikely. However, if thyroid hormone attached to receptors on the lumen surface of blood vessels nourishing the brain and subsequently altered microvascular flow, it might cause secondary effects in the brain without having crossed the barrier.

11. Kontos et al. (1965) showed that blood flow is markedly increased in skeletal muscle of thyrotoxic patients. Although oxygen consumption and carbon dioxide production were increased, the arteriovenous difference across skeletal muscle of patients was *reduced* relative to normals. Thus, the increased muscle flow was greater than needed for increased oxygen requirements. These observations are comprehensible if thyroid-induced metabolism changes are secondary to circulatory changes; they do not suggest that muscle circulation increases to sustain increased metabolism.

Summary

The concept that histamine serves as an intrinsic microcirculatory dilator may have important implications for the interpretation of thyroid hormone actions.

It is suggested that thyroid hormone participates in distribution of nutrients to cells of vertebrates by altering responsiveness of vascular smooth muscle to constrictors and dilators, for example, norepinephrine and histamine. From enhanced constriction of larger vessels and histamine-induced reflex vasodilatation of the arterial side, a circulatory pattern comprising open arterioles and precapillary sphincters, partially closed veins, and rapid heart action may cause a generalized expansion of capillary perfusion. The greater availability of nutrients may trigger metabolic activation of cells and produce extra energy and growth in immature homeotherms but only energy in adults. In cold acclimation, activation of sympathetic output as well as thyroid output occurs. Overperfusion may, therefore, be confined largely to heart, lung and skeletal muscle, thus increasing energy production but not the rate of growth. In tadpoles, a generalized increase in tissue perfusion may result in metabolite activation

of the many preset changes involved in metamorphosis. In frogs, however, since potential for growth and heat production is low, even large doses of thyroid hormone have little effect. Some of the symptoms of hypothyroidism—weakness, poor growth and development, cold intolerance, and metabolic disturbances—may result from impaired nutritive blood flow and inadequate cell nutrition.

Evidence favoring a primary circulatory action of thyroid hormone is presented; however, it is not implied that all thyroid hormone effects are derived from circulatory changes. Thyroxine is present in some plants and in certain lower animals. Whatever actions it may have in primitive forms may also be primary actions in higher animals.

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